Technology Assessment Program

Office of Patient Care Services

BRIEF OVERVIEW

EVIDENCE REVIEWS FOR MANAGEMENT OF ACUTE ISCHEMIC STROKE: THROMBOLYTIC THERAPY AND ORGANIZATION OF CARE

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A SUMMARY FOR HTA REPORTS
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VATAP is a member of the International Network of Agencies for Health Technology Assessment (INAHTA) [http://www.inahta.org]. INAHTA developed this checklist© as a quality assurance guide to foster consistency and transparency in the health technology assessment (HTA) process. VATAP will add this checklist© to its reports produced since 2002.

This summary form is intended as an aid for those who want to record the extent to which a HTA report meets the 17 questions presented in the checklist. It is NOT intended as a scorecard to rate the standard of HTA reports – reports may be valid and useful without meeting all of the criteria that have been listed.

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(AUGUST 2004)

Item	Yes	Partly	No
Preliminary			
1. Appropriate contact details for further information?	√		
2. Authors identified?	√		
3. Statement regarding conflict of interest?			√
4. Statement on whether report externally reviewed?	√		
5. Short summary in non-technical language?	√		
Why?			
6. Reference to the question that is addressed and context of the assessment?	√		
7. Scope of the assessment specified?	√		
8. Description of the health technology?		√	
How?			
9. Details on sources of information?	√		
10. Information on selection of material for assessment?	√		
11. Information on basis for interpretation of selected data?	√		
What?			
12. Results of assessment clearly presented?	√		
13. Interpretation of the assessment results included?	√		
What Then?			
14. Findings of the assessment discussed?	√		
15. Medico-legal implications considered?		√	
16. Conclusions from assessment clearly stated?	√		
17. Suggestions for further actions?	√		

TECHNOLOGY ASSESSMENT PROGRAM

An Effective Resource for Evidence-based Managers

VA's Technology Assessment Program (VATAP) is a national program within the Office of Patient Care Services dedicated to advancing evidence-based decision making in VA. VATAP responds to the information needs of senior VHA policy makers by carrying out systematic reviews of the medical literature on health care technologies to determine "what works" in health care. "Technologies" may be devices, drugs, procedures, and organizational and supportive systems used in health care. VATAP reports can be used to support better resource management.

VATAP has three categories of products directed toward meeting the urgent information needs of its VA clients. VATAP assigns a category to each new request based largely on the availability of studies from results of initial searches of peer-reviewed literature databases, and the client's information needs:

- The ***Short report*** is a self-contained, rapidly-produced qualitative systematic review of 5 to 20 pages in length. It provides sufficient background information and clinical context to its subject technology to be accessible to a wide audience, including non-clinician managers.

- The ***Brief overview*** originated as an internal memo to VA clients with both well-defined and urgent information needs. It usually comprises 2 to 10 pages and assumes sufficient existing knowledge regarding clinical context and technology issues by its readers to omit these components of other VATAP products. It often requires some additional reading of documents (provided to the client with the overview) to obtain a full and comprehensive picture of the state of knowledge on the topic.

- The ***Bibliography*** is a selection of quality-filtered references of about 3 to 5 pages in length, not subject to external review. In addition to a reference list, it includes a brief synopsis about the policy issue at hand, background on the topic to provide clinical context, and search and retrieval methodology, but it does not include in-depth analysis.

VATAP's physician advisor and/or key experts in VHA review all VATAP products. Additional comments and information on this report can be sent to:

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Notes:

- ***Abbreviations for (recombinant) Tissue Plasminogen Activator in this report are either TPA , rTPA, or rt-PA.***
- ***Where direct quotes from existing reviews are indicated by quotation marks and italics, VATAP adheres to the same abbreviation form as the original.***

BACKGROUND

Context and scope

The Veterans Health Administration (VHA) Office of Patient Care Services (OPCS) charged the VA Technology Assessment Program (VATAP) with identifying and forwarding for VHA clinical policy makers' appraisal existing evidence reviews relevant to VHA's ischemic stroke management policy, specifically the use of intravenous thrombolysis and the organization of acute care.

VHA's intent is that individual facilities have policies in place for swift evaluation of probable stroke patients by specialists; options for facilities include (Booss, 2004):

- Participating in a local EMT network in which all persons with acute stroke would go to a designated stroke center;
- Providing thrombolysis in house—meaning that the necessary studies and specialist personnel are available at all times to appropriately select, treat, and monitor patients;
- Accelerating relationships with an affiliated academic medical center.

The urgent information needs of OPCS prompted VATAP's two-stage response: 1) an initial package of evidence reports forwarded to OPCS for policy makers' review and synthesis within two weeks of the Program's charge, followed by 2) further retrievals and this brief overview.

In other words, this overview represents background to a selection of quality-screened evidence reviews for VHA policy makers' use. OPCS did not request a formal or comprehensive synthesis of existing evidence reviews. Finally, reviews addressing uncommon underlying mechanisms of stroke such as arterial dissection or dural sinus thrombosis were specifically excluded from the present report, as were reports from individual clinical research studies. In this context, the present report catalogs public domain reviews available to support VHA policy. It is intended to be neither comprehensive in its coverage of acute stroke management nor independent of the existing reviews (n. b. description of brief overview, page ii).

BURDEN OF DISEASE

Schellinger (2004) offers a succinct and current overview of the burden of stroke:

> *"Stroke is the third leading cause of death after myocardial infarction and cancer, and is the leading cause of permanent disability in western countries. Furthermore, it is the*

leading cause of disability-adjusted loss of independent life years. Aside from the tragic consequences for patients and their families, the socioeconomic impact of more or less disabled stroke survivors is evident, as stroke patients with permanent deficits such as hemiparesis and aphasia will frequently not be able to live independently or pursue an occupation. The added indirect and direct cost estimates for a survived stroke vary between US $35,000 and $50,000 per year. In the face of our aging population and the skewed population pyramid, the incidence and prevalence of stroke is expected to increase. Therefore, an effective treatment for this devastating disease is desperately needed."

Laloux (2003) confirms the devastation associated with stroke in a list of deficit frequencies after stroke: hemiparesis, in 70-80% of stroke survivors; ambulation problems, 70-80%; visual perception deficits, 60-75%; dysarthria, 55%; depression, 40%; aphasia, 20-35%; dysphagia, 20-35%; and alteration of recent memory, 10-20%. Age at time of stroke is correlated with residual deficit.

Stamm (1997) provides so focused a series of points on stroke within VHA that VATAP amends only to update with more recent data:

- *"Stroke is the nation's third leading cause of death, and the leading cause of serious long-term disability.*
- *There are about 13,500 strokes each year in VA* [current estimates are 10,900 and 11,558 stroke admissions per year in VHA for 2003 and 2004, respectively, recognizing that estimation accuracy is highly dependent on the method used (Marshall, 2004)].
- *Stroke and related diseases consume 5% of VHA resources.*
- *Certain veteran populations, such as POWs, and those with PTSD, have an increased risk of stroke.*
- *85% of strokes are ischemic, resulting from insufficient blood flow to the brain; 15% are hemorrhagic, resulting from bleeding into the brain.*
- *Stroke can be viewed as a "brain attack". Time is brain. Fast treatment helps stop tissue damage, save brain function, and reduce patient dependency.*
- *Antiplatelet drugs and some thrombolytics show new promise in reducing death and disability from stroke.*
- *Treatments must be chosen carefully because they have important trade-offs in benefits and harms.*
- *VA sponsored research has led to important advances in stroke prevention and recovery."*

VHA research in progress

Since 1997, VA Heath Services Research and Development Service (HSR&D) has planned and implemented the Quality Enhancement Research Initiative (QUERI), one focus of which is stroke (Oddone, 2000). These authors outline important areas in treatment and prevention of stroke for the veteran population:

- Preventing initial strokes;
- Improving outcomes for patients with stroke;
- Identifying post-stroke rehabilitation strategies that preserve function in the optimum setting.

State of knowledge

Publication of results of the National Institute of Neurological Disorders and Stroke (NINDS rTPA Stroke Study Group, 1995) trial of recombinant tissue plasminogen activator (rTPA) for acute stroke led the FDA to approve its use and professional associations to issue corresponding recommendations. However, subsequent trials failed to confirm NINDS results unequivocally (Devuyst, 2001) and unresolved issues regarding thrombolysis remain.

The QUERI stroke group plans to identify gaps in the existing knowledge base and propose recommendations for closing those gaps. While the results of such plans would be important to the present report, the QUERI stroke group has not yet published reports on its completed work. In the interim, van Gijn's (2004) outline of still-outstanding questions regarding TPA thrombolysis is directly relevant to VHA policy and its evolution to accommodate new research:

1. Is there worthwhile benefit when thrombolysis is given in non-specialist centers?
2. Which patients are most likely to suffer early hazard and which will gain the greatest long-term benefit?
3. How wide is the time window?
4. What is the best thrombolytic agent and the best dose?
5. Should patients receive anticoagulants or anti-platelet agents after intravenous thrombolysis?
6. How can administrative and organizational barriers be overcome?

Furlan, writing in 2002, confirmed the directions of new acute stroke therapy research:

- Newer thrombolytic agents are more fibrin-specific and have longer half-lives than tPA, but efficacy and safety research on the new agents was incomplete at the time of publication.
- New devices (catheter systems, angioplasty, or stents) and interventions (intra-arterial thrombolysis, or combinations of interventions) for opening blocked arteries are under investigation.
- Imaging techniques that provide more information than conventional CT are needed for better patient selection.

Hacke (2004) confirms that defining the optimal time after symptom onset for thrombolytic administration remains an issue sufficient to warrant further pooled, analyses of original trial data.

METHODS

Search strategy

This project required an extremely rapid response so VATAP performed MEDLINE searches exclusively. Searches covered 1990 to July 2004 using the MeSH descriptors: stroke units, acute stroke care, and thrombolytics as major search terms, along with publication types (review, meta-analysis, or clinical guideline). These were combined with free text words and MeSH terms for author names identified by means of initial searches. All searches were restricted to articles in English and adult human subjects.

Further, VATAP searched The Cochrane Library, the AHRQ National Guidelines Clearinghouse, and the health technology assessment (HTA) database maintained by the International Network of Agencies for Health Technology Assessment (INAHTA) using the search terms above for stroke to identify completed reports or projects in progress.

Selection criteria

On behalf of VHA stroke policy makers, VATAP elected to focus on systematic reviews of thrombolysis or aspects of care organization for acute stroke in humans. Reviews were further required to be available in English and published or updated since 2000. Clinical guidelines were eligible if their recommendations were based unequivocally on systematic reviews, as were articles reporting pooled or cumulative meta-analyses of randomized trials and economic analyses, which rely on systematically derived estimates of efficacy and costs. One author (KF) selected citations for full-text retrieval, reviewed all articles, abstracted critical information, and prepared this overview.

Systematic reviews

Cook (1997) and Mulrow (1997) define systematic reviews: *"Systematic reviews are scientific investigations in themselves, with pre-planned methods and an assembly of original studies as their "subjects". They synthesize the results of multiple primary investigations by using strategies that limit bias and random error…"* The same authors further specify characteristics of systematic reviews and contrast them with traditional narrative reviews that synthesize a selection of articles without reporting methods of selection or quality criteria.

Systematic reviews:

- Ask a focused clinical question;
- Conduct a comprehensive search for relevant studies using an explicit search strategy;
- Uniformly apply criteria for inclusion and exclusion of studies;
- Rigorously and critically appraise included studies;
- Provide detailed analyses of the strengths and limitations of included studies.

Systematic reviews can be quantitative (i.e., meta-analytic, applying statistical methods to the summary study results) or qualitative; in either case the inferences or conclusions of the review must follow logically from the evidence presented.

RESULTS

The searches outlined above identified 39 review citations available in English and published or updated from 2000 to 2004, of which 34 are independent reviews and five duplicate parts of other reviews. Reviews are categorized in Tables 1 and 2. Table 1 lists the topics in stroke care covered by other published reviews that may interest VHA decision makers.

As indicated in Table 2, 20 systematic reviews (eight for thrombolytics and five for organization of care; the remainder for other interventions) met VATAP eligibility criteria for forwarding to VHA decision makers. Table 2 also indicates that a further 19 narrative or non-systematic reviews covered the topics requested, but do not meet VATAP criteria for VHA policy makers' use. Tables 3 and 4 further detail conclusions and recommendations from the systematic reviews.

Table 1. Summary availability of stroke evidence reviews in English, published or updated 2000-2004

Topics	**Number of reviews**	
	Systematic	Narrative/non-systematic
Intravenous thrombolytics	8*	5
Organization of care	5*	3
Intra-arterial, other acute stroke interventions	2	3
Other topics in acute stroke	5	8
Totals	**20**	**19**

Shaded cells indicate the number of reviews meeting selection criteria for this overview

* Hacke (2003) appears in both sections.

Table 2. Categories and content of evidence reviews (published or updated 2000-2004, in English) retrieved by VATAP searches

Study type	Citation (systematic?)	Content
IV Thrombolytics		
Clinical guideline	Daniel Freeman Hospital (2002) **(no)**	Intravenous TPA in acute ischemic stroke
	Adams (2003) **(not strictly systematic, but provides some detail on methods and evidence grading criteria)**	Early management of patients with ischemic stroke
	Hacke (2003) (**systematic reviews plus consensus)**	Recommendations for stroke management: primary and secondary prevention; diagnostic imaging and emergency management; thrombolytics; organization of acute care and rehabilitation.
Systematic review	Wardlaw (2003)	Cumulative meta-analysis
	Sandercock (2002)	Thrombolytic therapy, neuroprotective agents, barriers to implementation in HNS
	Wardlaw (2001)	Overview of Cochrane thrombolysis meta-analysis
	Graham (2003)	Meta-analysis of safety data
	Sandercock (2004)	Cost-effectiveness model based on NHS costs (originally included in Sandercock 2002)
	Hacke (2004)	Pooled analysis of all major investigations of TPA for acute stroke: Is time to treatment a critical predictor of therapeutic benefit?
Narrative, non-systematic reviews	Lindsberg (2003)	Thrombolysis in community-based settings
	Klijn (2003)	Summary and comparison of ASA and EUSI guidelines
	Schellinger (2001a)	Intravenous thrombolysis
	Benchenane (2004)	Equivocal roles of TPA
Organization of care		
Clinical guidelines/ Recommendations	Alberts (2000)[Brain Attack Coallition (2000)] **(no)**	Establishment of primary stroke centers
Systematic reviews	Hacke (2003) **systematic reviews plus consensus**	Recommendations for stroke management, updated 2003: primary and secondary prevention; diagnostic imaging and emergency management; organization of acute care and rehabilitation.
	Brainin (2004)	Organization of care (EUSI guidelines)
	Cochrane stroke unit trialists' collaboration (2002)	Organized inpatient (stroke unit) care for stroke
	Kwan (Cochrane review, (updated 2004)	In-hospital care pathways for stroke
	Kwan (2004)	Improving efficiency of delivery of thrombolysis
Narrative, non-systematic reviews	Nunez (2004)	Organization of care
	Kennedy (2004)	Organization of local and regional stroke resources
Intra-arterial thrombolytics, other acute stroke interventions		

Study type	Citation (systematic?)	Content
Clinical guidelines	ASA (2002) **(yes)**	Anticoagulants and antiplatelet agents within 48 hours of symptom onset
Systematic review	Lisboa (2002)	Intra-arterial thrombolytic therapy
Narrative reviews	Van Gijn (2004)	Remaining uncertainties re TT
	Schellinger (2001b)	Intra-arterial thrombolysis, vertebrobasilar stroke, phase IV trials, stroke imaging
	Furlan (2002)	Recombinant pro-urokinase and intra-arterial thrombolysis
Other topics, new developments		
Overviews of meta-analyses	Ringleb (2002)	Thrombolytics 3-6 hours after onset
	Wardlaw (2001)	Cochrane thrombolysis meta analysis
Systematic reviews	McKevitt (2004)	Qualitative studies of "human impact " of stroke with implications for improving care
	Bays (2001)	QoL for stroke survivors
	Martinsson (Cochrane, 2003)	Amphetamines after stroke
Narrative reviews	Schellinger (2004b)	Selection criteria for TT > 3 hours after symptom onset.
	Schellinger (2003)	Imaging-based decision making in thrombolytic therapy
	Schellinger (2004a)	Update on thrombolytic therapy
	Xavier (2003)	Intra-arterial thrombolytics
	Wahlgren (2004)	Neuroprotective agent trials, with discussion about why animal model results have failed to translate to humans with stroke.
	Diaz (2004)	Recently identified risk factors for stroke
	Furlan (2002)	Impracticalities of tPA, newer thrombolytics and interventions
	Devuyst (2001)	Recent progress in drug treatment for acute stroke

ASA, American Stroke Association
EUSI, European Stroke Initiative
QoL, quality of life
TPA, tissue plasminogen activator
TT, thrombolytic therapy

SUMMARY OF FINDINGS: EVIDENCE REVIEWS

So much has been said, and so well, that VATAP concludes with a series of excerpts and commentary on the topics of interest to this overview. Should there be concerns that quotations have been taken out of context, the reader is again referred to the definition of VATAP's Brief Overview format (page ii), for reassurance that VHA policy makers have full-text copies of all systematic reviews included in the "Attachments" list on page 14, and thus may interpret context and conclusions for themselves.

Thrombolysis

While the doubts about efficacy versus risks and difficulties getting stroke patients to care fast enough that are mentioned earlier in this document no doubt persist, systematic reviews, and guideline developers relying on them, are consistent in their conclusions that thrombolysis with intravenous recombinant tissues plasminogen activator improves outcomes in carefully selected ischemic stroke patients (Tables 3 and 4). An economic analysis (Sandercock, 2004), using

efficacy estimates from Cochrane reviews and treating eligible patients up to six hours after symptom onset, concludes:

> *"Our analyses, based on an up-to-date estimate of the effectiveness of rt-PA and modeled on the NHS, suggest that rt-PA might well be cost-effective. In the base case analysis, treatment with rt-PA was associated with an additional cost of £13,581 per QALY gained during the first 12 months after treatment. This estimate was considerably higher than the published estimates for treatment with rt-PA for myocardial infarction, but it was still well within the range of cost-effectiveness for health care interventions offered within the NHS…When the model was run to the end of the cohort lifetime, there appeared to be a substantial cost savings of £96, 565 per QALY gained…"*

Organization of care

Schellinger (2004b) support the efficacy of thrombolysis and comment on problems with organization of care:

> *"After the publication of the National Institute of Neurological Disorders and Stroke (NINDS) study in 1995, thrombolytic therapy with recombinant tissue plasminogen activator was approved for treatment of acute stroke within a 3-hour time window after exclusion of intracerebral hemorrhage by non-contrast computed tomography. Currently in Europe and the United States, this effective therapy is given to approximately 1% to 2% of ischemic stroke patients. The percentage of patients given this therapy is so small because of several reasons, such as persisting doubts, fear of intracerebral hemorrhage, poorly organized services, or inadequate reimbursement, but most of all because of the late arrival of most patients. With implementation of an effective stroke care system, thrombolytic therapy can be administered in accordance with American Heart Association guidelines in up to 10% of patients in community hospitals and in up to 22% of all ischemic stroke patients in major urban stroke centers…"*

Langehorne (2004):

> *"…The updated systematic review* (the 1993 Cochrane review of stroke unit care)*, which now contains information on almost 5000 patients from 23 clinical trials, confirms that stroke patients who were managed in a stroke unit were less likely to die (3% absolute risk reduction), require institutional care (2% absolute reduction), or have long-term dependency (5% absolute reduction). Further corroboration of the benefits of stroke unit care has come from the National Stroke Register in Sweden (RIKS stroke project), which shows that patients who were admitted to a hospital with an organized stroke unit were more likely to survive and return home, even after adjusting for variations in case mix…*
>
> *The message from these studies is that the quality of stroke care is important. Stroke patients admitted to hospital should receive care that is organized within discreet stroke units staffed by a multidisciplinary team (medical, nursing, physiotherapy, plus occupational and speech and language therapies) with an interest and expertise in stroke care…."*
>
> *The next generation of stroke units should examine in randomized trials components of care, such as intensive monitoring of physiologic abnormalities, very early mobilization, novel strategies to detect and prevent complications, acute supportive therapies, and systems of rehabilitation. While we await the results of such research, clinicians and service planners should ensure that basic systems of stroke-unit care, whose benefit has been clearly demonstrated, are implemented."*

Schellinger (2004b) points out that extending the therapeutic time frame for thrombolytic therapy requires analysis of available efficacy data beyond three hours plus improvement of the diagnostic yield of current imaging techniques. These authors conclude that the literature at the time of their publication supports time windows of six and 12 hours for the anterior and posterior circulations, respectively.

Recombinant tissue plasinogen activator (TPA) is the only thrombolytic currently approved by FDA for use in acute stroke for persons who present to medical facilities within three hours of the onset of stroke symptoms.

Furlan (2002) outlines problematic areas related to use of TPA in his discussion of acute stroke therapy "*beyond IV tPA*":

- tPA is effective, but often impractical, given the three hour therapeutic window and the need for CT to rule out intracerebral hemorrhage.
- Intracerebral hemorrhage remains a problem after tPA administration.

The questions reported by Furlan in 2002 remain under active investigation but also still lack fully definitive answers:

- Newer thrombolytic agents are more fibrin-specific and have longer half-lives than tPA, but efficacy and safety research on the new agents was incomplete at the time of publication.
- New devices (catheter systems, angioplasty, or stents) and interventions (intra-arterial thrombolysis, or combinations of interventions) for opening blocked arteries are under investigation.
- Imaging techniques that provide more information than conventional CT are needed for better patient selection.

Benchenane (2004) confirms that the use of TPA to treat stroke in humans remains controversial, with only 1-6% of potentially eligible patients receiving treatment. Similar controversy surrounds organization of stroke care, particularly related to mechanisms for insuring that appropriate patients receive effective therapy (Jauch, 2004).

Klijn (2003) summarize agreement between two major guideline developers, the American Stroke Association and the European Union Stroke Initiative:

> *"Although transatlantic differences might create different interpretations, priorities, and views, the guidelines are remarkably similar, even regarding controversial issues. We believe this is not only because both groups have had the opportunity to discuss many of the controversial issues at international meetings, but also because both groups have endorsed the concept of evidence-based medicine and have based their recommendations on similar classifications of the level of evidence for the effectiveness of interventions. This is a triumph for evidence-based medicine and a major step towards unification of acute stroke management worldwide."*

The same authors go on to outline core challenges in stroke management:

> *"There are three major challenges in stroke management. To increase the body of reliable evidence from large randomized controlled trials of the safety, effectiveness and cot of promising treatments (e.g., thrombolysis, antithrombotic therapy, neuroprotection, in interventional recanalization, alone and in combination) in a wide range of patients around the world. To facilitate the widespread development of stroke units, delivery of organized stroke care, and emergency transport of patients with stroke to appropriate stroke centers. And finally, to improve the uptake of effective therapies into clinical practice…"*

Table 3. Recommendations of guidelines relevant to VHA policy

Guideline	Thrombolytic Therapy	Organization of care
American Stroke Association (Adams, 2003)	• "The NIHSS score can also help identify those patients at greatest risk for intracranial hemorrhage associated with thrombolytic treatment. In the NINDS trial of rtPA, those with a score of 20 or greater non the NIHSS had a 17% chance of intracranial hemorrhage, whereas the risk of bleeding was only 3% among those with a score < 10." (p. 1058-9). • "Intravenous rtPA (0.9mg/kg, maximum dose 90mg) is strongly recommended for carefully selected patients who can be treated within 3 hours of onset of ischemic stroke (grade A evidence)." (p. 1066) • "The decision for treatment with rtPA is based on several features (tabulate in Adams, 2003). The physician should review each of the criteria to determine the patient's eligibility….Patients with major stroke (NIHSS > 22) have a very poor prognosis whether or not they are treated with rtPA. Because of this, and because the risk of hemorrhage is considerable among this population, caution should be exercised. However, they may still benefit from treatment…." (p. 1066) • "… patients and their families should be informed or risks and benefits as with any other approved medical or surgical intervention." (p. 1066)	Not explicitly addressed in the guideline.
European Stroke Initiative (Hacke, 2003)	• "Intravenous rTPA (0.9mg/kg, maximum 90 mg), with 10% of the dose given as bolus followed by an infusion lasting 60 min, is the recommended treatment within 3h of onset of ischemic stroke. • The benefit from the use of IV rTPA beyond 3h after onset is smaller, but still present up to 4.5h. • IV rTPA is not recommended when the time of onset of stroke cannot be ascertained reliably; this includes persons whose strokes are recognized upon awakening. • IV administration of streptokinase is dangerous and not indicated for the management of persons with ischemic stroke. • Data on the safety and efficacy of any other intravenously administered thrombolytic drugs are not available to provide a recommendation. • Intra-arterial treatment of acute middle cerebral artery occlusion in a 6h time window using pro-urokinase results in significantly improved outcome. • Acute basilar occlusion may be treated with intra-arterial therapy in selected centers in an institutional protocol as experimental therapy or within a multi-center clinical trial. • Ancrod cannot presently be recommended for use in acute ischemic stroke outside the setting of clinical trials". (p.329)	• "Stroke patients should be treated in stroke units (stroke units should provide coordinated multidisciplinary care provided by medical, nursing, and therapy staff who specialize in stroke care). Therefore, suspected stroke patients should be transported without delay to the nearest medical center with an available stroke unit, or to a hospital providing organized stroke care if a stroke unit is not available. • Once stroke symptoms are suspected, patients or their proxies should call EMS or a similar system. • Patients with subarachnoid hemorrhage should be referred urgently to a center with facilities for neurosurgical treatment, neuroradiological interventions and neurointensive care. (p. 313-4)"

NIHSS, National Institutes of Health Stroke Scale (included in Adams, 2003)

Table 4. Systematic reviews: Abstracted reviews of thrombolysis and organization of acute stroke care, published in English, 2000-2004

Citation	Conclusions	Recommendations
Hacke (2003) [and Brainin 2004]	Over the past decades, acute stroke has increasingly been recognized as a medical emergency. Acute, post-acute, and rehabilitation of stroke patients in specialized wards as well as revascularizing therapies have been proven to be effective in acute ischemic stroke. Thrombolytic Therapy Intravenous rTPA Eight trials have tested rTPA in 2889 patients. Overall, there was a significant reduction in the number of patients with poor functional outcomes (combined death or dependency) at the end of follow-up (OR 0.83, 95% CI 0.73-0.94). The subgroup of patients treated within 3 hours showed a greater reduction in poor functional outcome (OR 0.58 95%CI .0.46-0.74) with no adverse effect on death. A pooled analysis of individual data of the 6 rTPA trials confirms that thrombolysis works at least until 4.5 h and potentially up to 6h after onset. Caution is advised before giving intravenous rTPA to persons with severe stroke (NIHSS > 25), or if CT demonstrates extended early changes of a major infarction, such as sulcal effacement, mass effect and edema. Intravenous administration of rTPA more than 3 h after stroke should only be given in an institutional protocol as experimental therapy or within a multi-center clinical trial. Continuous auditing of routine use of thrombolytic therapy is advisable. Safety monitoring of treatment is a condition of approval of rTPA in the European Union. Organization of care The establishment of a network consisting of acute stroke units, seamless continuation to post-acute care and rehabilitation, as well as further care in the community has become standard treatment in many European countries. Systems of care have emerged that include nation-wide concepts of stroke care units focusing on the acute care as in Austria or Germany, and systems of stroke units focusing on comprehensive care including rehabilitation as in the UK or Scandinavia.	Thrombolytic therapy • Intravenous rTPA (0.9mg/kg, maximum 90 mg), with 10% of the dose given as bolus followed by an infusion lasting 60 min, is the recommended treatment within 3h of onset of ischemic stroke. • The benefit from the use of IV rTPA beyond 3h after onset is smaller, but still present up to 4.5h. • IV rTPA is not recommended when the time of onset of stroke cannot be ascertained reliably; this includes persons whose strokes are recognized upon awakening. • IV administration of streptokinase is dangerous and not indicated for the management of persons with ischemic stroke. • Data on the safety and efficacy of any other intravenously administered thrombolytic drugs are not available to provide a recommendation. • Intra-arterial treatment of acute middle cerebral artery occlusion in a 6h time window using pro-urokinase results in significantly improved outcome. • Acute basilar occlusion may be treated with intra-arterial therapy in selected centers in an institutional protocol as experimental therapy or within a multi-center clinical trial. • Ancrod cannot presently be recommended for use in acute ischemic stroke outside the setting of clinical trials. Organization of care • Stroke patients should be treated in stroke units (stroke units should provide coordinated multidisciplinary care provided by medical, nursing, and therapy staff who specialize in stroke care). Therefore, suspected stroke patients should be transported without delay to the nearest medical center with an available stroke unit, or to a hospital providing organized stroke care if a stroke unit is not available. • Once stroke symptoms are suspected, patients or their proxies should call EMS or a similar system. • Patients with subarachnoid hemorrhage should be referred urgently to a center with facilities for neurosurgical treatment, neuroradiological interventions and neurointensive care. Emergency management: Minimum requirements for centers managing acute stroke patients: • Availability of 24-hour CT scanning. • Established stroke treatment guidelines and operational procedures. • Close cooperation of neurologists, internists and rehabilitation experts. • Specially trained nursing personnel. • Early multidisciplinary rehabilitation including speech therapy, occupational therapy and physical therapy. • Established network of rehabilitation facilities to provide a continuous process of care. • Neurosonological investigations within 24 h (extracranial vessels, color-coded duplex sonography). • ECG • Laboratory examinations (including coagulation parameters. • Monitoring of blood pressure, ECG, oxygen saturation, blood glucose, body temperature). • Additional recommendations on diagnostic imaging, emergent diagnostic tests, rehabilitation, and quality control of time frames for treatment of acute stroke.

Citation	Conclusions	Recommendations
Hacke (2004)	Pooled analysis of individual patient data from RCTs • Treatment was started within 360 minutes of onset of stroke in 2775 patients randomized to TPA or placebo at 300 hospitals (including community hospitals) in 18 countries: • Median age, 68 years; median baseline NIHSS, 11; median time to treatment, 243 minutes. • Patient eligibility for trials: clinical diagnosis of ischemic stroke determined by focal neurological deficit, clearly defined tine of stroke onset, and head CT excluding hemorrhage. Patients who awoke with symptoms of stroke were excluded or time of onset was defined as when they were last awake and had no symptoms. • Time from symptom onset to treatment was inversely correlated with baseline NIHSS score • Odds of favorable 3 month outcome increased as time to treatment decreased: 2.8 for 0-90 minutes; 1.6 for 91-180 minutes; 1.4 for 181-270 minutes; 1.2 for 271-360 minutes. • Hazard ratio for death adjusted for baseline NIHSS was not different from 1.0 for time intervals up to 270 minutes; for 271-360 minutes it was 1.45. • Hemorrhage: 5.9% of TPA patients and1.1% of controls p< 0.0001; Hemorrhage was not associated with time to treatment or baseline NIHSS score, but with TPA and age. • The analysis did not provide strong evidence to exclude patients from treatment based on baseline NIHSS for any time interval tested.	The sooner that TPA is given to stroke patients, the greater the benefit, especially if started within 90 minutes. Results of the pooled analysis suggest a potential benefit beyond 3 hours, but any benefit may be associated with risks. None of the individual trials treating patients beyond 3 h had sufficient power to detect effects of the magnitude expected. Additional large RCTs are under way to confirm a therapeutic window beyond 3 hours.
Adams (2003)	• Intravenous administration of rTPA is currently the only FDA-approved therapy for treatment of patients with acute ischemic stroke. • Its use is associated with improved outcomes in a broad spectrum of carefully selected patients who can be treated within 3 hours of onset of stroke. Earlier treatment (i.e., within 90 minutes) may be more likely to result in a favorable outcome. Later treatment, at 90 to 180 minutes, is also beneficial. • Treatment with rTPA is associated with symptomatic intracranial hemorrhage, which can be fatal. Management of intracranial hemorrhage following treatment with TPA is problematic. The best methods for preventing bleeding complications are careful selection of patients and scrupulous ancillary care. • Close observation and monitoring of the patient and early management of arterial hypertension are critical. The use of anticoagulants and anti-platelet agents should be delayed for 24 hours after treatment.	• The evaluation of patients with acute ischemic stroke should be performed immediately. The medical history and the general and neurological examinations form the cornerstone of emergent evaluation of patients with suspected ischemic stroke. The clinical evaluation provides clues about the cause of the neurological symptoms and screens for potential contraindications for treatment with thrombolytic agents. • Patients generally require a limited number of diagnostic tests as part of the emergent evaluation (tabulated in Adams, 2003). Because time is of the essence in acute stroke care, institutions should have these diagnostic studies available on a 24-h/day7-d/week basis. If the tests are not readily available, and if time and the patient's condition permit, the patient's transfer to another medical facility equipped to do so should be considered…. • Intravenous recombinant TPA (0.9mg/kg, maximum dose 90 mg) is strongly recommended for carefully selected patients who can be treated within 3 hours of onset of ischemic stroke. • The decision for treatment with TPA is based on several features (tabulated in Adams, 2003). Patients with major strokes (NIIHSS> 22) have a very poor prognosis whether or not they are treated with TPA. Because of this, and because the risk of hemorrhage is considerable among this population, caution should be exercised. However, they may still benefit from treatment. • To date, no other thrombolytic agent has been established as a safe and effective alternative to rTPA. Currently available data do not support the clinical use of either streptokinase or ancrod.
Graham (2003)	Meta-analysis of safety data from 15 open-label studies (10 prospective, 5 retrospective or mixed; 2639 patients) broadly following approved indications and guidelines for TPA in nonselective patient populations: • Median baseline NIHSS score: 14; • Symptomatic intracerebral hemorrhage rate: 5.2% (CI, 4.3-6.0), not significantly correlated with frequency of protocol deviations. • Mean total death rate: 13.4%; • Rate of very favorable outcome: 37.1%; • Protocol deviations reported in 19.8% of cases, overall; comparison across studies without adjustment for number of cases showed that mortality was correlated with percentage of protocol deviations (r = 0.67, p = 0.018 • If highest mortality, highest protocol deviation series is omitted, then correlation loses statistical significance.	"*Post approval data support the safety of intravenous thrombolytic therapy with tPA for acute ischemc stroke, especially when established treatment guidelines are followed.*

Citation	Conclusions	Recommendations
Wardlaw (2003)	Cumulative meta-analysis of thrombolytic agent trials published since 1992 (the year of publication of the first "modern trial" with a short time window): • 14 trials met inclusion criteria, although not all trials provided data for every outcome. • From 1992 to 2001, 2830 patients had received rTPA in trials. • Point estimate remains consistent from 1995 onwards, and CI narrows from a spread of 0.31 in 1995 to 0.22 in 1999. • For 1000 patients treated with rTPA up to 6 h after stroke, 55 (CI, 18-92) fewer would be dead or dependent at the end of follow-up. • There was significant heterogeneity between trials, but not between publication dates. • Estimates of SICH did not change materially over time from mid-1990s to later trials. o SICH occurred among 10% of patients allocated top rTPA (fatal in 4%) and among 3% of control patients (fatal in 1%), an absolute excess of 25 fatal ICH per 1000 patients treated. • ICH showed no heterogeneity between trials up to 6 hours, or between trial dates • Results of rTPA trials were consistent with those of other thrombolytic agents: Thrombolysis significantly reduced death or dependency compared with control: approximately 40 more alive and independent patients per 1000 treated.	
Sandercock(2002) [And Published: Sandercock, 2004]	Effectiveness, cost effectiveness, and barriers to implementation of thrombolytic and neuroprotective therapy for acute ischemic stroke in the NHS. Systematic review results: • Efficacy of thrombolysis: o 17 trials (5216 patients) of urokinase, streptokinase, recombinant TPA, or recombinant pro-urokinase were included; o 50% of data came from TPA trials, mostly given within 6 hours of stroke onset. o Thrombolytic therapy significantly increased odds (OR 4.5) of fatal intracerebral hemorrhage. o Abs increased odds of death at the end of follow-up (OR, 1.31). o Despite increase in deaths, thrombolytic therapy within 6 hours significantly reduced the proportion of patients who were dead or dependant at the end of follow up- (or, 0.83). o Heterogeneity between trials may be due to: the thrombolytic drug used, variation in concomitant use of aspirin and heparin, stroke severity, and time to treatment. The most widely tested agent, TPA, shows less hazard and more benefit than other agents. • Key barriers to acute stroke treatment: patient/family inability to recognize stroke symptoms or failure to seek urgent help; patient/family calls to general practitioner instead of ambulance; inefficient process of emergency stroke care in hospital; delay in neuroimaging. • Economic impact model suggest6ed that if eligible patients were treated with TPA there was a 78% probability of gain in quality adjusted survival during the first year at a cost of £13,582 per QALY gained. Over a life time, TPA was associated with a cost saving of £ 96,464 per QALY.	The evidence on thrombolysis does not support widespread unselective use of thrombolytic therapy for acute ischemic stroke in routine clinical practice in the NHS. Data on thrombolytic drugs are limited and estimates of effectiveness and cost effectiveness imprecise. The data were insufficient to estimate the cost of modifying NHS services to enable safe and effective delivery of rTPA.. A neuroprotective drug with even modest benefit is likely to be cost effective, but none is available. The cost of overcoming known barriers to acute stroke treatment is likely to vary by center and depend on the baseline level of stroke services.
Wardlaw (2001)	• Increase in odds of death within first 10 days (OR, 1.85; CI, 1.48-2.32) and symptomatic intracranial hemorrhage (OR, 3.53; CI, 2.79-4.45) with thrombolysis (slightly less with TPA). • The odds of death at the end of follow-up were also slightly increased with thrombolysis (OR, 1.13; CI, 1.13-1.52), although the increase was not significant in patients receiving TPA. • Despite this, there was a significant reduction in the number of patients with a poor functional outcome (death or dependency) at the end of follow-up (OR, 0.83;CI, 0.73-0.94), which was slightly better in patients receiving TPA.	A meta-analysis using individual patient data may be able to address the effect of thrombolysis in further specific subgroups and examine the interaction between severity of stroke and effect of thrombolysis.
Kwan (2004)	• 10 nonrandomized studies (too heterogeneous in design for meta-analysis) with 6345	Several programs were multi-faceted interventions, which might be more likely to be successful in reducing

Citation	Conclusions	Recommendations
	patients evaluated interventions that could speed up admission to hospital and administration of rTPA. • Types of intervention: o Public education to increase awareness of acute stroke symptoms and need to seek urgent help o training paramedical staff to improve accuracy of stroke diagnosis. o Helicopter transfer of patients to hospital. o Training in acute stroke therapy for emergency department staff. o Reorganization of in-hospital systems to streamline acute stroke care.	delays to therapy. However, no single intervention was identified that is most likely to increase access to, and use of, thrombolytic therapy for acute stroke. Several of the approaches covered might be able to be tailored to local circumstances and available resources. Implications for practice: • Although rTPA should be administered speedily, emergency physicians or stroke team must follow strict guidelines if it is to be administered safely and adverse effects minimized. • As patients with possible stroke arrive at hospital earlier, emergency physicians should be aware of increase chance for alternate diagnoses (TIA, intra-cerebral hemorrhage, non-stroke condition). • Observed effects of each intervention are specific to the local organizational setting and not generalizable to other hospitals or communities.
Kwan (Cochrane review 2004)	3 RCTs (340 patients) and 7 non-randomized studies (1673 patients): • no differences between care pathway and control groups for death, dependency, or discharge destination. • Non-randomized studies: patients managed using a care pathway may be less likely to suffer a urinary tract infection and be readmitted, and more likely to have a CT brain scan or carotid duplex study. • Randomized studies: patient satisfaction and QoL may be lower in the care pathway group.	
Stroke Unit Trialists (2002)	• 23 trials included. Compared to alternative services, stroke unit care: o reduced odds of death at final (median 1 year) follow-up o reduced odds of death or dependency o Subgroup analyses: benefits remained when analysis was restricted to truly randomized trials with blinded outcome assessment. o Outcomes were independent of patient age, sex and stroke severity, but appeared to be better in stroke units based in a discrete ward. • No indication that organized stroke unit care resulted in longer stay. • Stroke patients who receive organized inpatient care in a stroke unit are more likely to be alive, independent, and living at home one year after the stroke.	

Abbreviatons:
ASA, American Stroke Association
CI, 95% confidence interval
EUSI, European Union Stroke Initiative
OR, odds ratio
rTPA, (recombinant) tissue plasminogen activator
RCT, randomized controlled trial
SICH, symptomatic intracranial hemorrhage
QoL, quality of life
QALY, quality adjusted life year

ATTACHMENTS

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TECHNOLOGY ASSESSMENT PROGRAM

Mission Statement

To enhance the health of veterans and the nation by providing and fostering technology assessment for evidence-based health care

Values

Integrity and pride in the work that we do

Quality products that are clinically valid and methodologically transparent

Objectivity in evaluating and presenting research evidence

Commitment to continuous quality improvement and to the guiding principles of evidence based practices

Flexibility in responding to changes in VA and the larger healthcare environment

Innovation in designing products and their dissemination to best meet VA's needs

Accessibility of products and services